changes were also accompanied by increases in noncollagenous protein synthesis (total $^{14}$C-proline incorporated into lung tissue minus that incorporated into collagen), and, in females only, an increase in collagen production (% of total $^{14}$C-proline incorporated into collagen). Some parameters were also significantly increased in rats exposed to 6 mg/m$^3$ talc. While these results are consistent with the fibrosis observed histologically in rats, fibrosis was not seen histologically in mice.

Talc exposure was associated with a dose- and time-related impairment of respiratory functions in male and female rats. Although only slight trends were observed at 6 months in rats exposed to 18 mg/m$^3$ talc, functional alterations in rats at the high concentration were clearly evident after 11 months. In rats exposed to 6 mg/m$^3$, decrements in respiratory function were observed in males at 11 months and in males and females at 18 months. The functional impairment was characterized by reduced lung volumes and reduced dynamic and/or quasistatic lung compliance, indicating an increase in elastic recoil (increased lung stiffness). Further, reduced gas exchange efficiency and nonuniform intrapulmonary gas distribution were also observed. These changes are consistent with the multifocal fibrosis and inflammation that was centered around the centriacinar region of the lung.

Deposition of talc in the lungs of rats and mice produced an inflammatory response characterized primarily by the accumulation of alveolar macrophages and, to a lesser extent, neutrophils and monocytes within alveolar lumens. Smaller numbers of lymphocytes and plasma cells were also observed in the interstitial tissue surrounding airways, blood vessels, and alveolar septa. The lesions developed at the junction of the alveolar ducts and terminal bronchioles where particles of the size range used are known to be deposited (Brody and Roe, 1983). Although the inflammatory response was basically similar in rats and mice, there were important species differences. The lesions in rats were generally more extensive and more severe than those in mice at similar exposure concentrations. In rats, foreign body giant cells were occasionally seen and some of the alveolar macrophages developed the morphological characteristics of epithelioid macrophages. More importantly, the inflammatory lesions in rats were accompanied by interstitial fibrosis, hyperplasia of alveolar epithelial type II cells, and, infrequently, squamous metaplasia of the alveolar epithelium.

The differences in pulmonary response cannot be attributed to differences in lung talc burden, since fibrosis and alveolar epithelial hyperplasia were seen in rats exposed to 6 mg/m$^3$, which had lung talc burdens less than that of mice exposed to 18 mg/m$^3$. Saffiotti and Stinson (1988) have reported similar differences in pulmonary response between rats and mice following intratracheal instillation of silica. These authors found that silica-induced alveolar epithelial hyperplasia in mice was transient, returning to normal within several months, while that in rats was generally more severe and persisted until the end of the study. Since inhalation studies using both rats and mice are seldom performed, it is uncertain if this species difference might exist for other particulate substances.

The difference in pulmonary response between rats and mice may be related, in part, to species differences in reactivity of the alveolar macrophage following phagocytosis of the talc particles. As the principal phagocytic cell of the lung, the alveolar macrophage is believed to play a major role in the inflammatory and fibrogenic reactions to inhaled particles (Brain, 1980; Brody, 1991). Much of the early work in this area centered on the differential cytotoxicity of phagocytized particles, particularly the various crystalline forms of asbestos and silica, to alveolar macrophages and the subsequent release of lysosomal enzymes which have proteolytic, elastolytic, and inflammatory properties (Brody and Davis, 1982; Nathan, 1987). More recently, alveolar macrophages have been shown to produce arachidonic acid metabolites (Kouzan *et al.*, 1985) and various cytokines that regulate cell proliferation, differentiation, and extracellular matrix production (Kelley, 1990). Of particular interest, rat alveolar macrophages exposed to iron spheres and asbestos fibers have been shown to produce increased amounts of a homologue of platelet-derived growth factor (Bonner *et al.*, 1989, 1990), the most potent mitogen known for mesenchymal cells, and TGF-ß, a potent inhibitor of mesenchymal cell proliferation and stimulator of matrix production (Kalter *et al.*, 1989). Little is known about the putative role of PDGF and TGF-ß and other macrophage-derived products in the pathogenesis of lung disease, but they are likely to be important mediators of many cellular events.

The lesions in the lungs of rats exposed to aerosols of talc are very similar, qualitatively, to those reported to occur following long-term (approximately 2 years) exposure to other inorganic,

non-fibrous, particulate substances including titanium dioxide (Lee *et al.*, 1985), chromium dioxide (Lee *et al.*, 1988), antimony trioxide and antimony ore concentrate (predominantly antimony trisulfide) (Groth *et al.*, 1986), and volcanic ash (Wehner *et al.*, 1986). Aerosols of each of these particulate substances were reported to elicit pulmonary inflammation, characterized primarily by the accumulation of alveolar macrophages, hyperplasia and squamous metaplasia of the alveolar epithelium, and fibrosis. Since the various components of the pulmonary response were not quantified in these studies, there may be quantitative differences in the degree of inflammation, fibrosis, and cellular degenerative hyperplastic and metaplastic changes to these particulate substances.

The lesions in rats exposed to talc are also similar to those observed in rats exposed to silica, but with important differences. Silica generally produces an inflammatory response that is more pronounced and persistent than the response to the relatively more inert particles like titanium dioxide and talc (Saffiotti and Stinson, 1988; Driscoll *et al.*, 1990). Further, while only occasional multinucleated cells and epithelioid macrophages were seen in the cellular response to talc, rats exposed to silica develop discrete nodular aggregates of epithelioid macrophages with some multinucleated cells more typical of granulomatous inflammation.

The quantitative and qualitative differences in pulmonary toxicity to inhaled particles are likely related to their size, structure (amorphous, crystalline, and/or fibrous), surface chemistry, solubility (or durability), chemistry of soluble components, cytotoxicity, and other factors. While much of the research in this area has focused on asbestos (as well as other fibers) and silica, the same principles are likely to explain the differences in biological activity of other particulate substances. Although a complete discussion of these factors is beyond the scope of this report, some of the evidence is presented here.

A number of studies of the various forms of silicon dioxide have shown that amorphous silica produces the mildest, slowest developing pulmonary changes followed, in ascending order, by quartz, cristobalite and tridymite (Allison, 1977; Hemenway *et al.*, 1986). Amorphous silica generally lacks a detectable crystalline X-ray diffraction pattern, while, of the crystalline forms, quartz has a less ordered symmetry than cristobalite and tridymite. Moreover, stishovite, which lacks the tetrahedral structure of other forms of silica, also lacks the fibrogenicity and cytotoxicity of the other forms (Brieger and Gross, 1967).

In general, the ability of various forms of silica to elicit pulmonary fibrosis parallels their cytotoxicity *in vitro* to alveolar macrophages (Reiser and Last, 1979). Further, there is a correlation between cytotoxicity and hemolytic activity *in vitro* (Allison, 1977). The biochemical basis of macrophage cytotoxicity and hemolytic activity is not fully understood, but the surface of crystalline silica presents highly reactive hydroxyl groups of silicic acid residues (silanol) that act as proton-donors and may combine with constituents of cellular membranes (Langer and Nolan, 1986). Kaolinite (aluminum silicate), mica (potassium aluminum silicate), and talc (magnesium silicate) are also hemolytic *in vitro* (Narang *et al.*, 1977). Dissolution of silicic acid residues from kaolinite, mica, and talc reduces the toxicity of these particulates, supporting the hypothesis that the reactive hydroxyl groups play an important role in cytotoxicity and hemolytic activity.

Following phagocytosis of silica (Allison, 1977) or kaolinite (Brody and Davis, 1982) particles by alveolar macrophages, hydrolytic enzymes are released from secondary lysosomes apparently as a result of the interaction of the particles with the lysosomal membrane. While the release of lysosomal enzymes into the cytoplasm may be directly responsible for cell death, it is less clear to what extent lysosomal enzymes released from the cells contribute to the other pulmonary lesions. Certainly, the ability to kill alveolar macrophages (cytotoxicity) is likely to inhibit or delay removal of the particles from the lung, increase the lung burden, and allow other biological effects to occur.

As already mentioned, macrophages secrete a large number of molecules with a wide range of biological functions including polypeptide hormones or cytokines, complement components, coagulation factors, arachidonic acid and its metabolites, bioactive lipids (prostaglandins and leukotrienes), binding proteins, enzyme inhibitors, extracellular matrix or cell adhesion proteins, and others (for review see Nathan, 1987). Some, or perhaps many, of the apparent differences in the pulmonary response of rats to the various particulate substances may be related to the extent to which they cause cytotoxicity and nonspecific release of lysosomal enzymes or cause macrophages to secrete specific effector substances like the cytokines and inflammatory mediators.

Exposure of female rats to 18 mg/m$^3$ talc was associated with increased incidences of benign and malignant pulmonary neoplasms (alveolar/bronchiolar adenoma: 1/50, 0/48, 9/50; alveolar/bronchiolar carcinoma: 0/50, 0/48, 5/50; squamous cell carcinoma: 0/50, 0/48, 1/50). The overall incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in female rats of the high-concentration group was significantly ($P \leq 0.001$) greater than that of controls (1/50, 0/48, 13/50). The incidence of pulmonary neoplasms in female rats exposed to 18 mg/m$^3$ also greatly exceeds that of control females (8/529, 1.5%) in the NTP lifetime studies reported by Solleveld *et al.* (1984). While comparison with the historical controls from NTP lifetime studies has some limitations (e.g., the studies were conducted about a decade ago and are not contemporary), such a comparison provides some perspective. The increased incidence of pulmonary neoplasms in the 18 mg/m$^3$ female rats was considered clear evidence of carcinogenic activity based on a) the strength of the statistical evidence ($P \leq 0.001$), b) the increase in malignant as well as benign neoplasms, and c) comparison with lifetime historical controls.

In contrast to female rats, there was no increase in the incidence of pulmonary neoplasms in male rats or in male or female mice exposed to talc aerosols. While precise comparisons between studies of talc and other particulate substances cannot be made because of differences in route of administration (intratracheal versus inhalation), strain of rat used, and exposure duration, such comparison provides some perspective (Table 12). The predilection of female rats over male rats for developing pulmonary neoplasms has also been observed in 2-year inhalation studies of titanium dioxide (Lee *et al.*, 1985), chromium dioxide (Lee *et al.*, 1988), antimony trioxide and antimony ore concentrate (predominantly antimony trisulfide) (Groth *et al.*, 1986), volcanic ash (Wehner *et al.*, 1986), and quartz (Dagle *et al.*, 1986). Chromium dioxide, volcanic ash, antimony trioxide, and antimony ore concentrate induced pulmonary neoplasms only in female rats, whereas titanium dioxide and quartz induced pulmonary neoplasms in males and females with a preponderance of neoplasms in females.

The morphological types of neoplasms induced by the particulates in the studies cited above also vary somewhat. The neoplasms in female rats exposed to talc were primarily alveolar/bronchiolar adenomas and carcinomas, although one squamous cell carcinoma also occurred. In female rats exposed to antimony trioxide or antimony ore concentrate (Groth *et al.*, 1986), there were similar numbers of alveolar/bronchiolar neoplasms and squamous cell carcinomas (Table 12). Further, several scirrhous carcinomas were seen in antimony exposed rats. In female rats exposed to titanium dioxide (Lee *et al.*, 1985), the incidences of alveolar/bronchiolar neoplasms and squamous cell carcinoma were also similar, whereas all but one of the neoplasms in males were alveolar/bronchiolar neoplasms. In contrast, nearly all the pulmonary neoplasms induced by quartz (Dagle *et al.*, 1986), volcanic ash (Wehner *et al.*, 1986) or chromium dioxide (Lee *et al.*, 1988) were squamous cell (epidermoid) carcinomas.

The pathogenesis of pulmonary neoplasms induced by the relatively insoluble particulate substances, such as talc, is currently unknown. Although a genotoxic mechanism cannot be ruled out, there are several facts and lines of evidence to suggest that a direct effect of the particulate on the target cell genome is not involved. First, the insoluble nature of these particulates makes it unlikely that any chemical constituents will reach sufficient concentration to affect the target cells within the relatively short period between the time they are deposited on the alveolar surface and the time they are phagocytized. Further, although occasional alveolar epithelial cells have been observed to contain particles following intratracheal or inhalation exposure (Sorokin and Brian, 1975; Lee *et al.*, 1979), the vast majority of particles are rapidly phagocytized by alveolar macrophages, some within minutes of deposition in the lung (Lauweryns and Baert, 1974). It is also clear that physical characteristics (crystalline structure, fiber dimension) and surface chemistry (presence of reactive groups on the particle surface), rather than soluble chemical components, are principle determinants of tissue reaction, and perhaps for carcinogenicity. The carcinogenicity of many fibrous materials (fiberglass, attapulgite, silicon carbide, mineral wool, and potassium titanate) decreases as fiber diameter exceeds 2.5 $\mu$m and as fiber length decreases below 10 $\mu$m (Stanton and Wrench, 1972; Stanton *et al.*, 1977).

A potential mechanism for the development of pulmonary neoplasms associated with insoluble particulate substances is that the prolonged stimulus for cell replication, due not only to cell injury but to the release of mitogenic growth factors from alveolar macrophages, provides a favorable

TABLE 12
**Results of Selected Whole Body Inhalation Carcinogenicity Studies of Particulate Materials**

| Compound and Dose | Study Duration | Species | Effects[a] |
|---|---|---|---|
| Talc at 0, 6, or 18 mg/m$^3$ (NTP, 1992) | Male: 113 weeks Female: 122 weeks | F344/N rats | Females: alveolar/bronchiolar adenoma (1/50, 0/48, 9/50); alveolar/bronchiolar carcinoma (0/50, 0/48, 5/50); squamous cell carcinoma (0/50, 0/48, 1/50) |
| Titanium dioxide at 0, 10, 50, or 250 mg/m$^3$ (Lee *et al.*, 1985) | 104 weeks | CD rats | Females: alveolar/bronchiolar adenoma (0/77, 0/75, 0/74, 13/74); squamous cell carcinoma (0/77, 0/75, 0/74, 13/74) |
| Titanium tetrachloride at 0, 0.1, 1.0, or 10 mg/m$^3$ (Lee *et al.*, 1986) | 104 weeks | Crl:CD rats | Females: squamous cell carcinoma (0/77, 0/75, 0/79, 3/75); Males: squamous cell carcinoma (0/79, 0/77, 0/78, 2/75) |
| Chromium dioxide at 0, 0.5, 0.5[b], or 25 mg/m$^3$ (Lee *et al.*, 1988) | 104 weeks | Sprague-Dawley rats | Females: squamous cell carcinoma (0/106, 0/103, 0/108, 2/108); keratin cyst (0/106, 0/103, 0/108, 6/108) |
| Antimony trioxide at 0 or 45 mg/m$^3$ (Groth *et al.*, 1986) | 73 weeks | Wistar rats | Females: alveolar/bronchiolar neoplasms (0/90, 11/90); squamous cell carcinoma (0/90, 9/90); scirrhous carcinoma (0/90, 5/90) |
| Antimony trisulfide at 0 or 40 mg/m$^3$ (Groth *et al.*, 1986) | 72 weeks | Wistar rats | Females: alveolar/bronchiolar neoplasms (0/90, 6/90); squamous cell carcinoma (0/90, 9/90); scirrhous carcinoma (0/90, 4/90) |
| Volcanic ash at 0, 5, or 50 mg/m$^3$ (Wehner *et al.*, 1986) | up to 104 weeks | F344 rats | Females: several[c] squamous cell carcinomas in the 50 mg/m$^3$ group. Male: one squamous cell carcinoma in the 50 mg/m$^3$ group. |
| Quartz at 0 or 50 mg/m$^3$ (Wehner *et al.*, 1986) | up to 104 weeks | F344 rats | Females: moderate[c] numbers of squamous cell carcinomas in the 50 mg/m$^3$ group. Males: one squamous cell carcinoma in the 50 mg/m$^3$ group. |

[a] Tumor incidences are given as the number of animals with tumor per number of animals examined. The incidences are given in the order of increasing exposure concentration.
[b] This dose represents unstabilized chromium dioxide; the other doses represent stabilized chromium dioxide.
[c] Precise numbers not available in journal article.

environment for the promotion and progression of spontaneously initiated cells. The interim evaluations in the NTP talc study clearly demonstrate a progressive impairment of homeostatic growth regulation in the areas of chronic inflammation and fibrosis associated with talc deposition in rats. Hyperplasia of the alveolar epithelium was evident at 6 months and became more extensive and severe with duration of exposure. Not only were there increased numbers of cells (hyperplasia), but some cells assumed morphologic features atypical of regenerating or differentiated type II cells (epithelial dysplasia). The altered or dysplastic epithelium was particularly evident in areas of fibrosis. The squamous metaplasia observed in female rats also represents altered differentiation of populations of alveolar epithelial cells and is notable in light of the development of squamous cysts and squamous cell carcinomas.

The lack of a carcinogenic effect in male rats or in mice exposed to talc aerosols does not negate the possibility of a mechanism as described above. First, the difference between male and female rats may be one of magnitude rather than an absolute difference in effect. The influence of the length of exposure on the development of these late appearing lung neoplasms cannot be discounted; the length of

exposure was 113 weeks for males and 122 weeks for females. Further, the promotion and progression of neoplasia involve a complex series of molecular events that are likely to differ qualitatively or quantitatively in males and females. Clearly, there are sex differences in the incidence of spontaneous and chemically induced neoplasms. As for mice exposed to talc, there was no histologic evidence of impaired growth regulation or fibrosis, consistent with the mechanism proposed above.

Pheochromocytomas (benign, malignant, or complex) of the adrenal medulla occurred with significant positive trends in both male and female rats exposed to talc (males: 26/49, 32/48, 37/47; females: 13/48, 14/47, 23/49). Further, the numbers of male and female rats with bilateral pheochromocytomas were also increased in the exposed groups. The overall incidences of this neoplasm in the 18 mg/m$^3$ exposure groups were significantly greater than those of the controls. Comparison with historical controls of NTP lifetime studies is not considered relevant, since there has been a pronounced increase in the spontaneous occurrence of pheochromocytomas in male rats in studies conducted by the NTP over the last 10 years (Rao *et al.*, 1990).

In contrast to the pheochromocytomas, the incidences of adrenal medulla hyperplasia in exposed male rats were lower than in controls, and the incidences were similar in all female groups. Because of the small size of the adrenal medulla, pheochromocytomas tend to obscure much or all of the remaining tissue. Therefore, the lower incidences of hyperplasia in groups of exposed males can be attributed, in part, to the larger number of pheochromocytomas.

While the increased incidences of pheochromocytomas in male rats were exposure related, it was believed to represent some, rather than clear, evidence of carcinogenic activity because a) the increase was associated primarily with benign neoplasms and b) there was no supporting increase in the incidence of hyperplasia. The increased incidence of pheochromocytomas in female rats was also exposure related.

Although the strength of the statistical association indicates that the pheochromocytomas are exposure related, a plausible mechanism for their increased occurrence in rats exposed to talc aerosols is not readily apparent. Since talc is relatively insoluble, it is extremely unlikely that any soluble components could have reached concentrations high enough in the blood to affect the adrenal medulla cells. Although purely speculative, there are two general hypotheses that might be considered. First, the increased incidence of adrenal pheochromocytomas may be a nonspecific effect of stress as a result of the chronic pulmonary inflammation. The body is known to respond to an exogenous challenge such as injury, inflammation, or infection by a set of distinct physiologic, metabolic, and endocrine changes including increases in serum adrenocorticotrophic hormone and cortisone levels, growth hormone, and catecholamine synthesis. Further, the adrenal medulla, as a modified sympathetic ganglia, reacts to neural as well as hormonal stimuli in the secretion of catecholamines. While prolonged stimulus of secretion is coupled with cellular hypertrophy and hyperplasia (cell proliferation) in many endocrine tissues, it is unknown if this occurs in the adrenal medulla. Moreover, if prolonged stress were to increase the rate of occurrence or growth of medullary proliferative lesions, similar exposure-related increases in pheochromocytoma incidence might be expected in other chronic toxicity and carcinogenicity studies. This has not generally been the case. Exposure-related increased incidences of pheochromocytoma were either not observed or not reported in the 2-year inhalation studies of other particulate substances reported above.

A second hypothesis to consider is that cytokines (growth factors), released from macrophages or other cells in the lung, might be responsible for increasing the rate of growth of pheochromocytomas. Although alveolar macrophages have been shown to secrete a number of cytokines known to stimulate proliferation of a variety of cell types, cytokines are generally believed to affect cells only in close proximity within the same organ. However, it has recently been shown that measurable levels of hepatocyte growth factor are present in the plasma after two-thirds hepatectomy (Lindroos *et al.*, 1992). Thus, some cytokines or growth factors may have wider effects than currently known.

## CONCLUSIONS

Under the conditions of these inhalation studies, there was *some evidence of carcinogenic activity** of talc in male F344/N rats based on an increased incidence of benign and malignant pheochromocytomas of the adrenal gland. There was *clear evidence of carcinogenic activity* of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of

the lung and benign and malignant pheochromocytomas of the adrenal gland. There was *no evidence of carcinogenic activity* of talc in male or female B6C3F$_1$ mice exposed to 6 or 18 mg/m$^3$.

The principal toxic lesions associated with inhalation exposure to talc in rats included chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous metaplasia and squamous cysts, and interstitial fibrosis of the lung. These lesions were accompanied by impaired pulmonary function characterized primarily by reduced lung volumes, reduced dynamic and/or quasistatic lung compliance, reduced gas exchange efficiency, and nonuniform intrapulmonary gas distribution. In mice, inhalation exposure to talc produced chronic inflammation of the lung with the accumulation of alveolar macrophages.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.

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# APPENDIX A
# SUMMARY OF LESIONS IN MALE RATS IN THE LIFETIME INHALATION STUDY OF TALC

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc[a]

| | 0 mg/m$^3$ | 6 mg/m$^3$ | 18 mg/m$^3$ |
|---|---|---|---|
| **Disposition Summary** | | | |
| Animals initially in study | 50 | 50 | 50 |
| Early deaths | | | |
| Moribund | 23 | 19 | 20 |
| Natural deaths | 18 | 17 | 14 |
| Survivors | | | |
| Died last week of study | 1 | 2 | 3 |
| Terminal sacrifice | 8 | 12 | 13 |
| Animals examined microscopically | 49 | 50 | 50 |
| **Alimentary System** | | | |
| Intestine large, cecum | (42) | (38) | (37) |
| Intestine large, colon | (43) | (43) | (46) |
| Intestine small, duodenum | (48) | (44) | (46) |
| Intestine small, ileum | (39) | (34) | (35) |
| Intestine small, jejunum | (40) | (38) | (40) |
| Liver | (49) | (50) | (48) |
| Neoplastic nodule | | | 1 (2%) |
| Neoplastic nodule, multiple | 2 (4%) | 1 (2%) | 3 (6%) |
| Osteosarcoma, metastatic, multiple, bone | 1 (2%) | | |
| Hepatocyte, adenoma | | 1 (2%) | |
| Mesentery | (2) | | (1) |
| Pancreas | (48) | (46) | (47) |
| Salivary glands | (49) | (50) | (50) |
| Fibroma | | 1 (2%) | |
| Stomach, forestomach | (49) | (47) | (47) |
| Fibrosarcoma | | | 1 (2%) |
| Stomach, glandular | (49) | (47) | (47) |
| Fibrosarcoma | | | 1 (2%) |
| **Cardiovascular System** | | | |
| Heart | (49) | (50) | (50) |
| **Endocrine System** | | | |
| Adrenal gland, cortex | (49) | (49) | (48) |
| Adrenal gland, medulla | (49) | (48) | (47) |
| Osteosarcoma, metastatic, uncertain primary site | | | 1 (2%) |
| Pheochromocytoma malignant | 2 (4%) | 3 (6%) | 6 (13%) |
| Pheochromocytoma complex | | 2 (4%) | 1 (2%) |
| Pheochromocytoma benign | 13 (27%) | 9 (19%) | 20 (43%) |
| Bilateral, pheochromocytoma malignant | 1 (2%) | | 1 (2%) |
| Bilateral, pheochromocytoma benign | 12 (24%) | 21 (44%) | 16 (34%) |
| Islets, pancreatic | (47) | (41) | (43) |
| Adenoma | 1 (2%) | | 2 (5%) |
| Carcinoma | 1 (2%) | | |
| Parathyroid gland | (45) | (45) | (46) |
| Adenoma | | 1 (2%) | |
| Pituitary gland | (47) | (50) | (49) |
| Pars distalis, adenoma | 12 (26%) | 11 (22%) | 10 (20%) |
| Pars distalis, carcinoma | | 1 (2%) | |
| Pars intermedia, adenoma | | | 2 (4%) |

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc (continued)

| | 0 mg/m$^3$ | 6 mg/m$^3$ | 18 mg/m$^3$ |
|---|---|---|---|
| **Endocrine System** (continued) | | | |
| Thyroid gland | (45) | (46) | (46) |
| C-cell, adenoma | 3 (7%) | 4 (9%) | 3 (7%) |
| C-cell, carcinoma | | 1 (2%) | |
| Follicular cell, adenoma | | | 1 (2%) |
| **General Body System** | | | |
| Tissue NOS | (1) | (1) | |
| Pheochromocytoma malignant, metastatic, adrenal gland | | 1 (100%) | |
| **Genital System** | | | |
| Epididymis | (49) | (50) | (49) |
| Preputial gland | (48) | (49) | (48) |
| Adenoma | 1 (2%) | 1 (2%) | 1 (2%) |
| Carcinoma | 1 (2%) | 6 (12%) | 1 (2%) |
| Prostate | (49) | (45) | (48) |
| Seminal vesicle | (49) | (48) | (47) |
| Testes | (49) | (50) | (50) |
| Bilateral, interstitial cell, adenoma | 18 (37%) | 24 (48%) | 24 (48%) |
| Interstitial cell, adenoma | 13 (27%) | 15 (30%) | 12 (24%) |
| **Hematopoietic System** | | | |
| Bone marrow | (48) | (48) | (47) |
| Lymph node | (49) | (50) | (50) |
| Lymph node, bronchial | (41) | (48) | (49) |
| Lymph node, mandibular | (46) | (48) | (47) |
| Lymph node, mediastinal | (48) | (49) | (47) |
| Lymph node, mesenteric | (49) | (48) | (47) |
| Spleen | (49) | (50) | (48) |
| Fibrosarcoma | 1 (2%) | | |
| Fibrous histiocytoma | | 1 (2%) | |
| Osteosarcoma, metastatic, bone | 1 (2%) | | |
| Thymus | (48) | (40) | (43) |
| Thymoma malignant | 1 (2%) | | |
| **Integumentary System** | | | |
| Mammary gland | (45) | (48) | (50) |
| Adenocarcinoma | 1 (2%) | | |
| Skin | (48) | (50) | (50) |
| Basosquamous tumor malignant | | | 1 (2%) |
| Fibroma | | 2 (4%) | |
| Fibrous histiocytoma | | | 1 (2%) |
| Keratoacanthoma | | 2 (4%) | 2 (4%) |
| Neurofibroma | | 1 (2%) | |
| Squamous cell carcinoma | | 1 (2%) | |
| Subcutaneous tissue, fibroma | | 1 (2%) | |
| Subcutaneous tissue, fibrosarcoma | | 1 (2%) | |
| Subcutaneous tissue, schwannoma malignant | 1 (2%) | | |

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc (continued)

| | 0 mg/m$^3$ | 6 mg/m$^3$ | 18 mg/m$^3$ |
|---|---|---|---|
| **Musculoskeletal System** | | | |
| Bone | (49) | (50) | (50) |
| Pelvis, osteosarcoma | | 1 (2%) | |
| Scapula, osteosarcoma | 1 (2%) | | |
| Vertebra, osteosarcoma | | | 1 (2%) |
| Skeletal muscle | (1) | | |
| **Nervous System** | | | |
| Brain | (49) | (50) | (50) |
| Astrocytoma malignant | 1 (2%) | | |
| **Respiratory System** | | | |
| Lung | (49) | (50) | (50) |
| Alveolar/bronchiolar adenoma | | 1 (2%) | 1 (2%) |
| Alveolar/bronchiolar carcinoma, multiple | | | 1 (2%) |
| Fibrosarcoma, metastatic, salivary glands | 1 (2%) | | |
| Osteosarcoma, metastatic | | 1 (2%) | |
| Osteosarcoma, metastatic, uncertain primary site | | | 1 (2%) |
| Osteosarcoma, metastatic, multiple, bone | 1 (2%) | | |
| Nose | (49) | (48) | (47) |
| Chondroma | 1 (2%) | | |
| Sarcoma | | 1 (2%) | |
| **Special Senses System** | | | |
| None | | | |
| **Urinary System** | | | |
| Kidney | (49) | (49) | (48) |
| Renal tubule, carcinoma | 2 (4%) | | |
| Urinary bladder | (49) | (48) | (47) |
| Papilloma | 1 (2%) | | |
| **Systemic Lesions** | | | |
| Multiple organs[b] | (49) | (50) | (50) |
| Leukemia mononuclear | 24 (49%) | 21 (42%) | 23 (46%) |
| Lymphoma malignant lymphocytic | 1 (2%) | | |
| Mesothelioma benign | 1 (2%) | | |
| Mesothelioma malignant | | | 1 (2%) |

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the Lifetime Inhalation Study of Talc (continued)

| | 0 mg/m$^3$ | 6 mg/m$^3$ | 18 mg/m$^3$ |
|---|---|---|---|
| **Tumor Summary** | | | |
| Total animals with primary neoplasms[c] | 48 | 49 | 50 |
| Total primary neoplasms | 116 | 135 | 137 |
| Total animals with benign neoplasms | 42 | 45 | 45 |
| Total benign neoplasms | 78 | 96 | 98 |
| Total animals with malignant neoplasms | 34 | 33 | 33 |
| Total malignant neoplasms | 38 | 39 | 39 |
| Total animals with metastatic neoplasms | 2 | 2 | 1 |
| Total metastatic neoplasms | 4 | 2 | 2 |
| Total animals with malignant neoplasms, uncertain primary site | | | 1 |

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Number of animals with any tissue examined microscopically
[c] Primary tumors: all tumors except metastatic tumors

TABLE A2
**Individual Animal Tumor Pathology of Male Rats in the Lifetime Inhalation Study of Talc: 0 mg/m³**

| Number of Days on Study | 3 3 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7<br>3 6 2 5 6 8 9 9 2 2 3 3 5 5 7 8 8 9 0 0 0 0 2 3<br>4 0 9 1 8 6 0 3 2 8 1 5 0 6 0 2 2 8 0 0 4 9 4 9 |
|---|---|
| **Carcass ID Number** | 3 3 3 3 4 2 2 3 3 4 3 3 3 4 3 3 3 3 3 3 3 2 4<br>6 0 6 4 1 9 9 1 8 2 3 4 6 1 4 4 4 1 1 8 9 1 9 1<br>1 0 8 0 3 4 5 8 7 0 9 2 3 8 5 3 8 7 6 5 0 3 6 4<br>1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 |
| **Alimentary System** | |
| Esophagus | + + + + + + + + + + + + + + + + + + + + + + + |
| Intestine large | + + + + + + + + + + + + + A + + + + + + + + + |
| Intestine large, cecum | + + + + + + + + + + + + + A + + + + + + + + + |
| Intestine large, colon | + + + M + + + + + + + + + A + + + + + + + + + |
| Intestine large, rectum | M + + + + + + + + M + + + A M + + + + + + + + |
| Intestine small | + + + + + + + + + + + + + + + + + + + + + + + |
| Intestine small, duodenum | + + + + + + + + + + + + + + + + + + + + + + + |
| Intestine small, ileum | A + + + + + + + + + + + + A + + A + + + + A + A |
| Intestine small, jejunum | A + + + + + + + + + + + + A + + A + + + + + + A |
| Liver | + + + + + + + + + + + + + + + + + + + + + + + |
| Neoplastic nodule, multiple | X |
| Osteosarcoma, metastatic, multiple, bone | X |
| Mesentery | + |
| Pancreas | + + + + + + + + M + + + + + + + + + + + + + + |
| Salivary glands | + + + + + + + + + + + + + + + + + + + + + + + |
| Stomach | + + + + + + + + + + + + + + + + + + + + + + + |
| Stomach, forestomach | + + + + + + + + + + + + + + + + + + + + + + + |
| Stomach, glandular | + + + + + + + + + + + + + + + + + + + + + + + |
| **Cardiovascular System** | |
| Blood vessel | + |
| Heart | + + + + + + + + + + + + + + + + + + + + + + + |
| **Endocrine System** | |
| Adrenal gland | + + + + + + + + + + + + + + + + + + + + + + + |
| Adrenal gland, cortex | + + + + + + + + + + + + + + + + + + + + + + + |
| Adrenal gland, medulla | + + + + + + + + + + + + + + + + + + + + + + + |
| Pheochromocytoma malignant | X |
| Pheochromocytoma benign | X X X X X |
| Bilateral, pheochromocytoma malignant | |
| Bilateral, pheochromocytoma benign | X X |
| Islets, pancreatic | + + + + + + + + + M + + + + + + + + + + + + + |
| Adenoma | |
| Carcinoma | |
| Parathyroid gland | + + + + + + + + + + + + + + + + + + M + + + + |
| Pituitary gland | + + + + + + + + + + + + I + + + + I + + + + + |
| Pars distalis, adenoma | X X X X X X |
| Thyroid gland | + + + + + + + + + + + + A + + + + + + + + + + |
| C-cell, adenoma | X |

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined